Synthesis and Properties of 1,3-Dimethyl-6-azalumazines
(Isofervenulins)

Fumio Yoneda, Tomohisa Nagamatsu,[1a] Kazuko Ogiwara,
Michiko Kanahori, Sadao Nishigaki,[1b]
and Edward C. Taylor[1c]

Pharmaceutical Sciences, Kumamoto University,[1a] Pharmaceutical
Institute, School of Medicine, Keio University[1b] and
Department of Chemistry, Princeton University[1c]

A new synthesis of 1,3-dimethyl-6-azalumazines (isofervenulins) is described. The reaction of 6-amino-1,3-dimethyl-5-nitrosouracil (I) with acid hydrazides in refluxing aprotic solvents such as dimethylformamide (DMF), dimethyl sulfoxide (DMSO) or sulfolane affords the corresponding 1,3-dimethyl-6-azalumazines (II) along with by-products, 2,4,9,11-tetramethyl-8-azapurino[7,8-f]-6-azapteridine-1,3,10,12(2H,4H,9H,-11H)-tetrones (III). These 8-azapurino[7,8-f]-6-azapteridines were alternatively prepared by the condensation of II with 6-amino-1,3-dimethyluracil in refluxing DMF. Compounds II were converted into 8-substituted theophyllines (V) by reductive ring contraction with sodium dithionite in formic acid.

Keywords——6-azapteridine; 6-azalumazine; 8-azapurino[7,8-f]6-azapteridine; ring contraction; theophylline

The antibiotic toxoflavin[2,3] and fervenulin,[4-11] derivatives of the pyrimido[5,4-e]-as-triazine (7-azapteridine) ring system, are of interest because of their close structural similarity to the naturally-occurring and physiologically active pteridines and purines, and because of their demonstrated antimicrobial activity. The isomeric pyrimido[4,5-e]-as-triazine (6-aza-pteridine) system has also become of interest[12-25] because of antiviral activity discovered in

1) Location: a) 5-1, Oe-honmachi, Kumamoto, 862, Japan; b) 35, Shinanomachi, Shinjuku-ku, Tokyo, 160, Japan; c) Princeton, New Jersey 08540, U.S.A.
2) G.D. Daves, R.K. Robins, and C.C. Cheng, J. Am. Chem. Soc., 84, 1724 (1962); and references cited therein.
3) F. Yoneda and T. Nagamatsu, Chem. Pharm. Bull. (Tokyo), 23, 2001 (1975).
4) G.D. Daves, R.K. Robins, and C.C. Cheng, J. Org. Chem., 26, 5256 (1961).
5) W. Pfleiderer and K.H. Schündehütte, Ann., 615, 42 (1958).
6) E.C. Taylor and F. Sowinski, J. Am. Chem. Soc., 90, 1374 (1968).
7) F. Yoneda, M. Kanahori, K. Ogiwara, and S. Nishigaki, J. Heterocyclic Chem., 7, 1443 (1970).
8) G. Blankenhorn and W. Pfleiderer, Chem. Ber., 105, 3334 (1972).
9) E.C. Taylor and F. Sowinski, J. Org. Chem., 40, 2321 (1975).
10) F. Yoneda and T. Nagamatsu, Bull. Chem. Soc. Jpn., 48, 2884 (1975).
11) M. Ichiba, K. Senga, S. Nishigaki, and F. Yoneda, J. Heterocyclic Chem., 14, 175 (1977).
12) L. Heinisch, W. Ozegowski, and M. Mühlstadt, Chem. Ber., 97, 5 (1964).
13) L. Heinisch, Chem. Ber., 98, 3095 (1965).
14) L. Heinisch, Chem. Ber., 100, 893 (1967).
15) E.C. Taylor and R.W. Morrison, J. Am. Chem. Soc., 87, 1976 (1965).
16) E.C. Taylor and S.F. Martin, J. Org. Chem., 35, 3792 (1970).
17) F. Yoneda, M. Kanahori, and S. Nishigaki, J. Heterocyclic Chem., 8, 523 (1971).
18) M. Brugger, H. Wamhoff, and F. Korte, Ann., 758, 173 (1972).
19) E.C. Taylor and S.F. Martin, J. Org. Chem., 37, 3958 (1972).
20) F. Yoneda, Y. Sakuma, M. Ueno, and S. Nishigaki, Chem. Pharm. Bull. (Tokyo), 21, 926 (1973).
21) T. Sugimoto and S. Matsuura, Bull. Chem. Soc. Jpn., 48, 725 (1975).
22) T. Sugimoto and S. Matsuura, Bull. Chem. Soc. Jpn., 48, 1679 (1975).
23) E.C. Taylor and F. Sowinski, J. Org. Chem., 40, 2329 (1975).
24) C. Küchler, W. Küchler, and L. Heinisch, Arzneimittel-Forsch., 16, 1122 (1966).
25) F. Yoneda, Kagaku no Ryoiki, 24, 1077 (1970).

this series.[24,25] For example, 7-ethylmercapto-1,3-dimethyl-6-azalumazine inhibited influenza A PR 8-virus and vaccinia virus.[24]
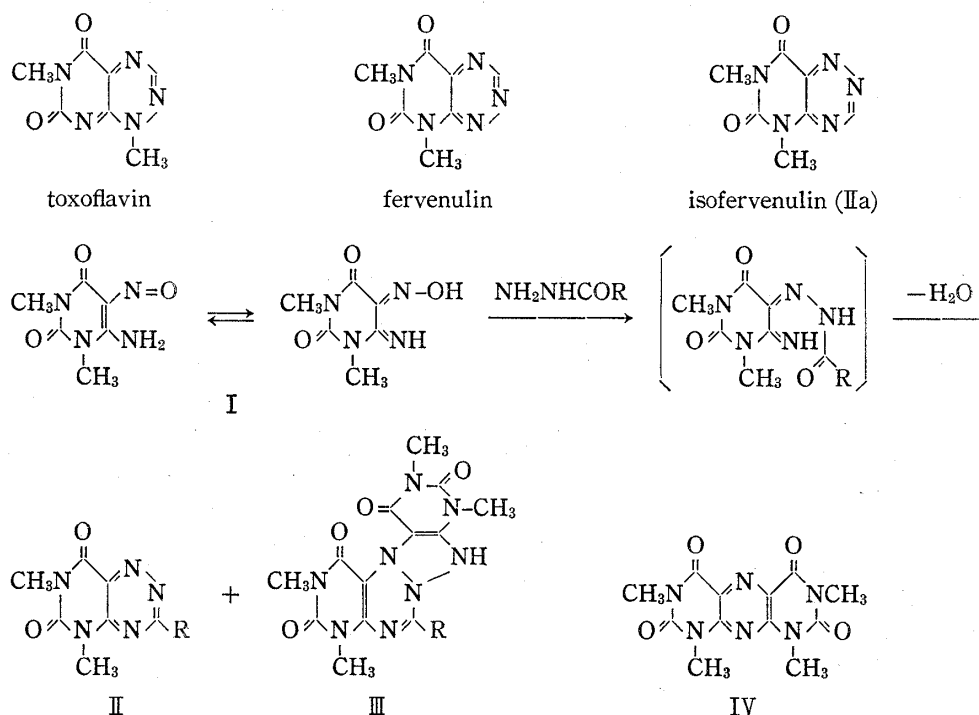

Chart 1

We now report a simple, one-step 6-azalumazine synthesis which consists of treatment of 6-amino-1,3-dimethyl-5-nitrosouracil (I) with acid hydradizes.[26] For example, heating I with a stoichiometric amount of formylhydrazine in dimethylformamide (DMF) afforded 1,3-dimethyl-6-azalumazine (isofervenulin) (IIa)[23] in about 15% yield, along with a small amount of 2,4,9,11-tetramethyl-8-azapurino[7, 8-f]-6-azapteridine-1,3,10,12($2H,4H,9H,11H$)-tetrone (IIIa). When dimethylsulfoxide (DMSO) or sulfolane was employed as solvent, the main product was 1,3,7,9-tetramethylpyrimido[5,4-g]pteridine-2,4,6,8($1H,3H,7H,9H$)-tetrone (IV). Formation of IV by partial thermal denitrosation of I, followed by condensation between the resulting 1,3-dimethyl-6-aminouracil and unchanged I, is well-known.[27] Condensation of I with several other acid hydrazides under similar conditions gave 7-substituted 1,3-dimethyl-6-azalumazines (IIc—g) along with the corresponding 8-azapurino [7,8-f]-6-azapteridines (IIIc—g). However, condensation of I with acethydrazide in DMF or DMSO gave only the insoluble 8-azapurino[7, 8-f]-6-azapteridine (IIIb) along with a trace of IV.

It is known that under certain conditions 6-amino-5-nitrosopyrimidines undergo reactions characteristic of oximes rather than nitroso compounds;[28-30] this also appears to be the case in the above condensation of I with acid hydrazides, and is apparently favored by the use of aprotic solvents. For example, fusion of I with acid hydrazides, or the use of acetic acid as solvent, led only to the symmetrical IV.

26) A part of this work was reported at the fourth international symposium on pteridines, Toba, 1969; see F. Yoneda, K. Ogiwara, M. Kanahori, S. Nishigaki, and E.C. Taylor in "Chemistry and Biology of Pteridines," ed. by K. Iwai, M. Akino, M. Goto, and Y. Iwanami, International Academic Printing Co., Ltd., Tokyo, 1970, pp. 145—153.
27) E.C. Taylor and E.E. Garcia, *J. Am. Chem. Soc.*, **97**, 4721 (1964).
28) E.C. Taylor and C.W. Jefford, *J. Am. Chem. Soc.*, **84**, 3744 (1962).
29) W. Pfleiderer and F.E. Kempter, *Angew. Chem.*, **79**, 234 (1967).
30) W. Pfleiderer and F.E. Kempter, *Angew. Chem.*, **79**, 234 (1967).

Representative examples are given in Table I. Yields of products differ according to slight changes in reaction conditions and it was difficult to obtain constant yields. Separation of the reaction products was easily achieved by concentration of the reaction mixture to a

TABLE I.   Preparation of 1,3-Dimethyl-6-azalumazines (Isofervenulins) (II) and
8-Azapurino[7,8-*f*]-6-azapteridines (III) from I and Acid Hydrazides

Substituent (R)	Reaction conditions			Products	
	Solvent	Time (hr)	Temp (°C)	Yield (%) of II	Yield (%) of III
H	DMF	6	170	15	4
Me	DMF	6	170	0	36
	DMSO	10	200	0	27
Ph	DMF	12	170	26	10
	DMSO	2	200	20	8
	Sulfolane	5	250	29	25
2-Furyl	DMF	12	170	21	5
	DMSO	2	200	16	1
2-Thienyl	DMF	8	170	23	3
	DMSO	2	200	15	1
3-Pyridyl	Sulfolane	2	250	36	14
4-Pyridyl	DMF	3	170	27	10
	Sulfolane	1	250	44	5

TABLE II.   UV Absorptions of Isofervenulins (II)

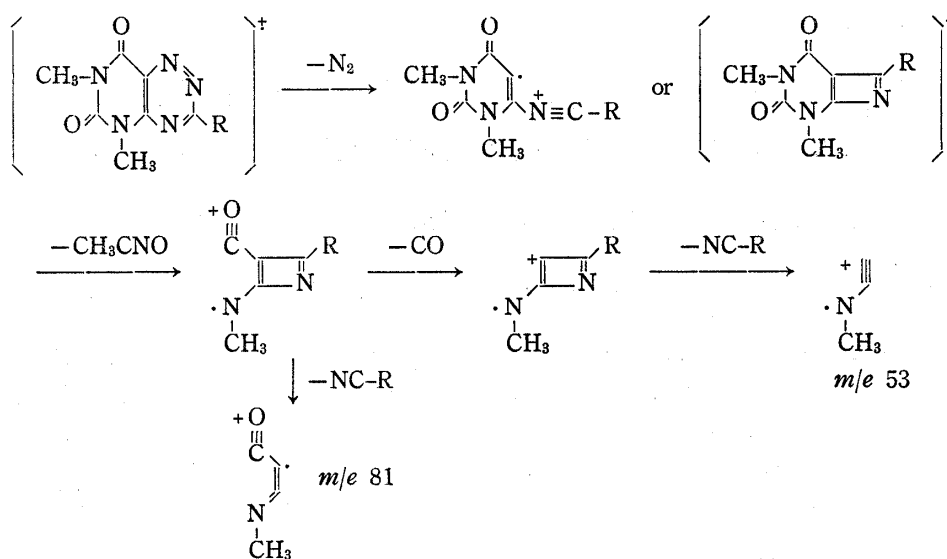| Compd. No.	R	λ_{max}^{EtOH} nm (log ε)
IIa	H	239.6(4.28), 311.5(3.85)
IIc	Ph	246.5(4.46), 331.0(4.25)
IId	2-Furyl	244.0(4.41), 351.0(4.42)
IIe	2-Thienyl	246.3(4.50), 354.0(4.54)
IIf	3-Pyridyl	240.0(4.43), 327.0(4.10)
IIg	4-Pyridyl	234.5(4.62), 324.0(4.24)
Fervenulin[3]		238 (4.27), 340 (3.62)
1,3-Dimethyllumazine[31] *a)*		236 (4.19), 331 (3.88)

a) Measured at pH 6.0.   Ph=phenyl

Chart 2

small volume, cooling to precipitate the insoluble by-product (III), and dilution of the filtrate with methanol.

Table II gives ultraviolet absorption data for 1,3-dimethyl-6-azalumazine derivatives, as well as for fervenulin[4] and 1,3-dimethyllumazine.[31] It is interesting to note that introduction of nitrogen into the 6-position of 1,3-dimethyllumazine shifts the longest absorption band from 331 nm to 311.5 nm. On the other hand, introduction of nitrogen into the 7-position (compare 1,3-dimethyllumazine with fervenulin) results in a red shift to 340 nm.
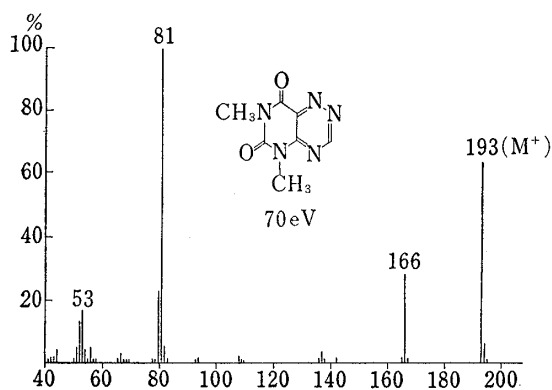

Fig. 1.   Mass Spectrum of 1,3-Dimethyl-6-azalumazine (IIa)

The most intense peak in the mass spectrum (MS) of 1,3-dimethyl-6-azalumazine and its 7-substituted derivatives (II) is at m/e 81. The second most intense peak is the molecular ion except in the case of the 7-phenyl derivative (see Fig. 2). Initial expulsion of nitrogen is the predominant and most characteristic mode of decomposition of a 1,3-dimethyl-6-azalumazine molecular ion. Although no metastable peaks are observed, several common patterns permit some generalization about the fragmentation mechanism, and this is illustrated in Chart 2. Only the 7-unsubstituted derivative (isofervenulin) is exceptional; here HCN is
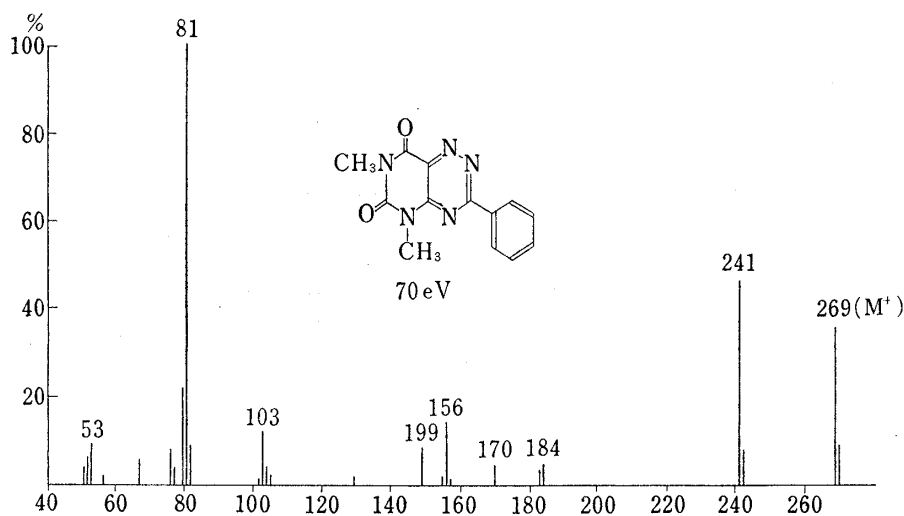

Fig. 2.   Mass Spectrum of 1,3-Dimethyl-7-phenyl-6-azalumazine (IIc)

initially lost. Fig. 1 and 2 show the mass spectra of isofervenulin (IIa) and its 7-phenyl derivative (IIc).

The assigned structures of by-products (III) as 2,4,9,11-tetramethyl-8-azapurino[7, 8-f]-6-azapteridine-1,3,10,12($2H,4H,9H,11H$)-tetrones were derived on the basis of elemental analyses, molecular weights as determined by mass spectrometry, the presence of N–H absorption (3180 cm^{-1} region) in their infrared spectra, the presence of four N-methyl groups in their nuclear magnetic resonance (NMR) spectra and by consideration of their probable mode of formation. The reaction presumably is initiated by nucleophilic attack of 6-amino-1,3-dimethyluracil (formed by denitrosation of I) on the electron deficient N-5 of the preformed

31) W. Pfleiderer, Chem. Ber., 90, 2582 (1957).

1,3-dimethyl-6-azalumazines (II).[32] Intramolecular cyclization of the resulting adduct and subsequent dehydrogenation would then yield III.

To confirm this, we have examined the condensation of II with 6-amino-1,3-dimethyluracil; for example, refluxing IIc with 6-amino-1,3-dimethyluracil in DMF gave IIIc in 70% yield.

Treatment of the above isofervenulin derivatives (II) with sodium dithionite in formic acid gave 8-substituted theophyllines (V), whose structures were established by comparison with authentic samples prepared by an alternative route.[33]
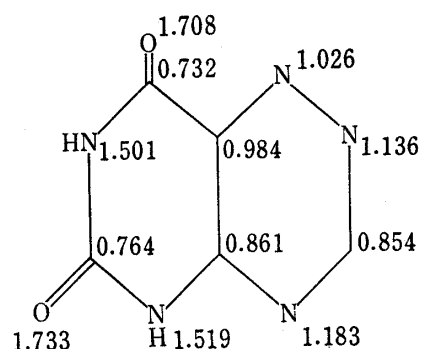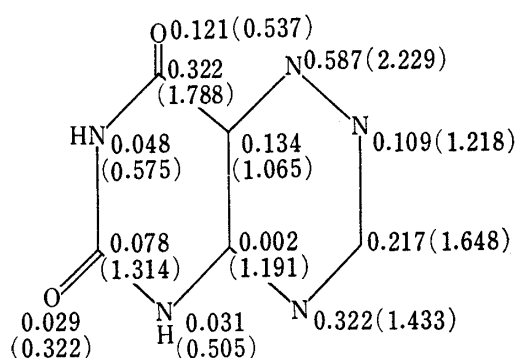
Fig. 3. π-Electron Distributions

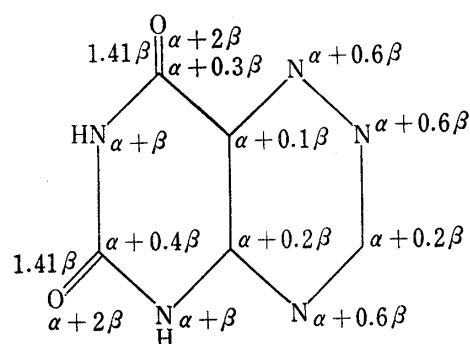Fig. 4. Frontier Electron Distributions and (Superdelocalizabilities)

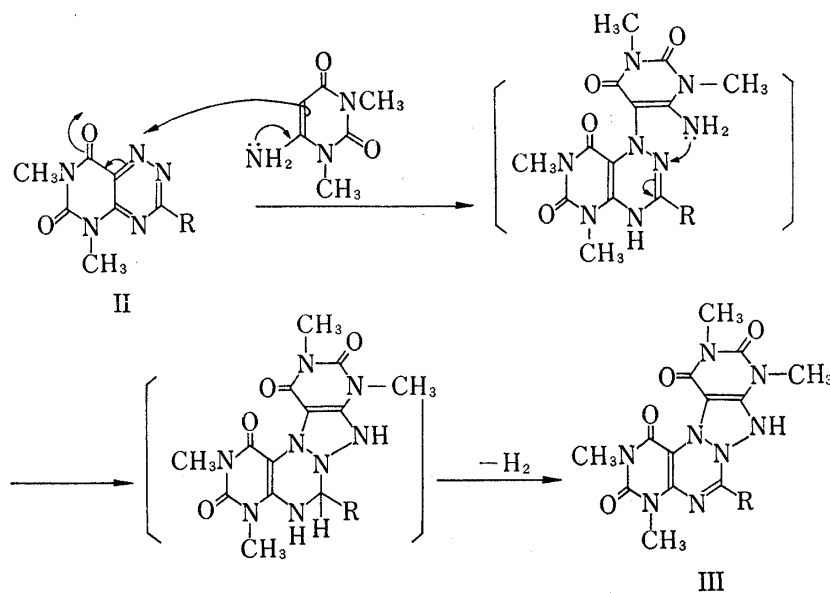Fig. 5. The Parameters used in Calculation

II

III

Chart 3

32) Fig. 3 and 4 show π-electron distributions of 1,3-dimethyl-6-azalumazine, and frontier electron distributions and superdelocalizabilities for reaction with nucleophiles calculated by a simple LCAO-MO method. The parameters used in these calculations are shown in Fig. 5. As can be seen from Figs 3 and 4, the most reactive site of II for nucleophilic addition is N-5.

33) F. Yoneda, K. Ogiwara, M. Kanahori, and S. Nishigaki, *J.C.S. Chem. Commun.*, **1970**, 1068.

The ring contraction observed in the conversion of isofervenulins to 8-substituted theophyllines is best rationalized by assuming initial reductive nitrogen–nitrogen bond cleavage to a 5-amino-6-amidinouracil, followed by intramolecular cyclization with elimination of ammonia. A remarkable solvent effect was noted during these reductive studies; heating of the above isofervenulins with sodium dithionite in DMSO resulted solely in the formation of IV.

Chart 4
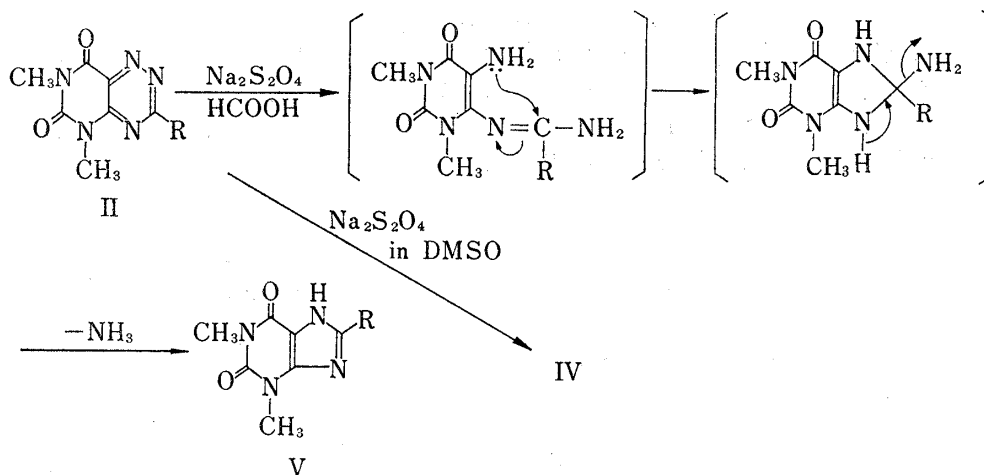
Experimental[34]

1,3-Dimethyl-6-azalumazine (Isofervenulin) (IIa)——A mixture of I (0.9 g, 0.005 mol) and formylhydrazine (0.3 g, 0.005 mol) in DMF (25 ml) was heated under mild reflux for 6 hr. The reaction mixture was evaporated to dryness and the residue was recrystallized from benzene to remove the less soluble 8-azapurino[7,8-f]-6-azapteridine (IIIa) as a yellow microcrystalline powder, MS m/e: 346 (M+). The filtrate

TABLE III.   7-Substituted 1,3-Dimethyl-6-azalumazines (Isofervenulins)
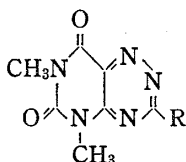
Compd. No.	R	mp (°C)	Recrystn. solvent	MS m/e (M+)	Formula	Analysis (%) Calcd.			Analysis (%) Found		
						C	H	N	C	H	N
IIa	H	199—200	MeOH	193	$C_7H_7N_5O_2$	43.52	3.65	36.26	43.28	3.71	36.32
IIc	Ph	239—240	MeOH or Benzene	269	$C_{13}H_{11}N_5O_2$	57.98	4.12	26.01	58.23	4.34	25.75
IId	2-Furyl	275—276	MeOH or CHCl$_3$	259	$C_{11}H_9N_5O_3$	50.96	3.50	27.02	51.29	3.73	26.77
IIe	2-Thienyl	249—250	MeOH or CHCl$_3$	275	$C_{11}H_9N_5O_2S$	47.99	3.30	25.44	47.94	3.56	25.30
IIf	3-Pyridyl	245	EtOH	270	$C_{12}H_{10}N_6O_2$	53.33	3.73	31.10	53.21	3.84	31.29
IIg	4-Pyridyl	292—295	EtOH	270	$C_{12}H_{10}N_6O_2$	53.33	3.73	31.10	53.31	3.68	30.88

34) All melting points were uncorrected.   NMR spectra were determined with a JEOL JNM 3H-60 spectrometer (tetramethylsilane as internal standard).   Identity of compounds was confirmed by comparison of infrared (IR) spectra (Nujol mulls) with a JASCO IR-1A spectrophotometer.
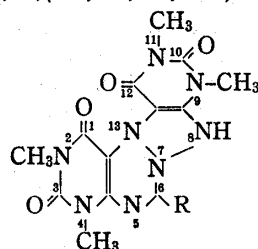
was evaporated to dryness and the residue was recrystallized from methanol to give isofervenulin (IIa),
mp 209—210° (lit.[23] 212°), NMR (DMSO-d_6) δ: 3.35 (s, N–Me), 3.49 (s, N–Me) and 9.66 (s, C-7 H).

When this reaction was carried out in DMSO or sulfolane at 200° for 2 hr, 1,3,7,9-tetramethylpyrimido-[5,4-g]pteridine-2,4,6,8(1H,3H,7H,9H)-tetrone (IV),[27] mp>360°, was obtained almost exclusively in 30% yield.

7-Substituted 1,3-Dimethyl-6-azalumazines (IIc—g). General Procedure——A mixture of I (1.8 g, 0.01 mol) and an acid hydrazide (0.01 mol) in DMF (45 ml), DMSO (40 ml) or sulfolane (20 ml) was heated under the conditions indicated in Table I. The reaction mixture was concentrated to a small volume and cooled to precipitate the less soluble by-product, the 8-azapurino[7,8-f]-6-azapteridine (III). The filtrate was diluted with methanol and allowed to stand overnight to separate the corresponding 1,3-dimethyl-6-azalumazine (II). These products were recrystallized from appropriate solvents.

Alternative Synthesis of 8-Azapurino[7,8-f]-6-azapteridines (III). General Procedure——A mixture of a 1,3-dimethyl-6-azalumazine (II) (0.01 mol) and 6-amino-1,3-dimethyluracil (0.01 mol) in DMF (50 ml) was refluxed for 10 hr, and the reaction mixture was concentrated to a small volume. The crystals thus separated were filtered off and recrystallized from appropriate solvents to give III as yellow crystals in 60—70% yields.

TABLE IV. 2,4,9,11-Tetramethyl-8-azapurino[7,8-f]-6-azapteridine-1,3,10,12,(2H,4H,9H,11H)-tetrones

Compd. No.	R	mp (°C)	Recrystn. solvent	MS m/e (M⁺)	Formula	Calcd. C	Calcd. H	Calcd. N	Found C	Found H	Found N
IIIa	H	>330	MeOH	346	$C_{13}H_{14}N_8O_4$	45.08	4.08	32.36	45.12	4.19	32.28
IIIb	Me	>330	CHCl₃	360	$C_{14}H_{16}N_8O_4$	46.66	4.48	31.10	46.48	4.43	30.87
IIIc	Ph	>330	CHCl₃	422	$C_{19}H_{18}N_8O_4$	54.02	4.30	26.53	53.93	4.35	26.46
IIId	2-Furyl	>330	CHCl₃	412	$C_{17}H_{16}N_8O_5$	49.51	3.91	27.18	49.52	3.90	27.01
IIIe	2-Thienyl	>330	CHCl₃	428	$C_{17}H_{16}N_8O_4S$	47.68	3.76	26.14	48.00	4.12	26.22
IIIf	3-Pyridyl	>330	DMF	423	$C_{18}H_{17}N_9O_4$	51.06	4.05	29.78	50.94	4.03	29.52
IIIg	4-Pyridyl	>330	DMF	423	$C_{18}H_{17}N_9O_4$	51.06	4.05	29.78	51.16	4.12	29.85

Conversion of 1,3-Dimethyl-6-azalumazines (II) into Theophyllines (V). General Procedure——A mixture of II (0.002 mol) and Na₂S₂O₄ (5.2 g, 0.03 mol) in 90% HCOOH (30 ml) was heated as indicated in Table V. After cooling, the precipitated crystals were filtered off, washed with H₂O and recrystallized from DMF to give the corresponding 8-substituted theophyllines (V), which were in all respects identical with authentic samples prepared by an alternative route.[33]

TABLE V. Conversion of 7-Substituted 1,3-Dimethyl-6-azalumazines (II) into
8-Substituted Theophyllines (V) by Reductive Ring Contraction
with Sodium Dithionite in Formic Acid

Compd. No.	Sub-stituent (R)	Reaction Time (hr)	Reaction Temp (°C)	Yield (%)	mp (°C)	Formula	Calcd. C	Calcd. H	Calcd. N	Found C	Found H	Found N
Vc	Ph	15	180	50	>330	$C_{13}H_{12}N_4O_2$	60.93	4.72	21.87	60.77	4.59	21.65
Vd	2-Furyl	7	160	38	>330	$C_{11}H_{10}N_4O_3$	53.66	4.09	22.76	53.72	4.15	22.44
Ve	2-Thienyl	7	160	39	>330	$C_{11}H_{10}N_4O_2S$	50.37	3.84	21.36	50.22	3.78	21.26
Vf	3-Pyridyl	6	180	56	>330	$C_{12}H_{11}N_5O_2$	56.02	4.31	27.23	56.13	4.33	27.09
Vg	4-Pyridyl	6	180	68	>330	$C_{12}H_{11}N_5O_2$	56.02	4.31	27.23	56.20	4.27	27.34